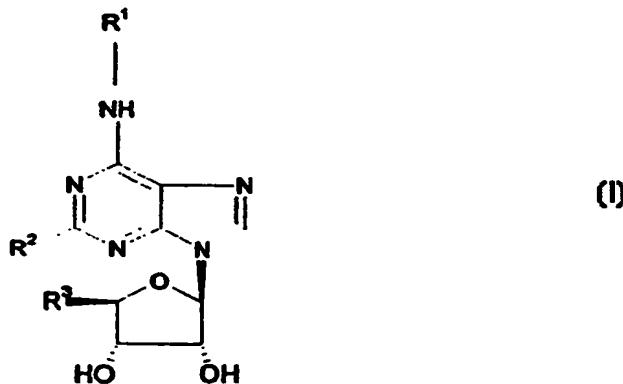


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :  C07H 19/00		A2	(11) International Publication Number: <b>WO 99/24449</b>  (43) International Publication Date: 20 May 1999 (20.05.99)
(21) International Application Number: PCT/EP98/07021			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 6 November 1998 (06.11.98)			
(30) Priority Data: 9723589.9 8 November 1997 (08.11.97) GB			
(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): COUSINS, Richard, Peter, Charles [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COX, Brian [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). ELDRED, Colin, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PENNELL, Andrew, Michael, Kenneth [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).			
(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			

## (54) Title: CHEMICAL COMPOUNDS



## (57) Abstract

A compound of formula (I) which is an agonist at the adenosine A1 receptor wherein R<sup>2</sup> represents C<sub>1</sub>-3alkyl, halogen or hydrogen; R<sup>3</sup> represents a fluorinated straight or branched alkyl group of 1-6 carbon atoms and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof. These compounds are agonists at the Adenosine A1 receptor.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

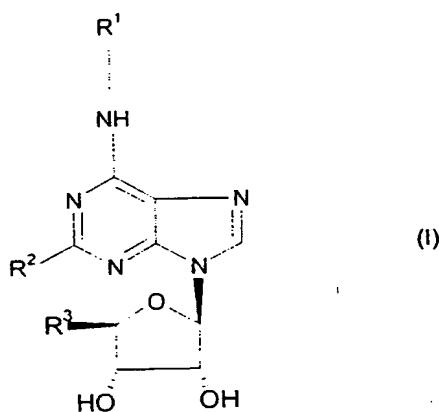
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CHEMICAL COMPOUNDS

The present invention relates to novel adenosine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their 5 use in medicine.

Thus the invention provides compounds of formula (I) which are agonists at the adenosine A1 receptor

10



wherein R<sup>2</sup> represents C<sub>1-3</sub>alkyl, halogen or hydrogen;

15

R<sup>3</sup> represents a fluorinated straight or branched alkyl group of 1-6 carbon atoms;

R<sup>1</sup> represents a group selected from

20 (1) -(alk)<sub>n</sub>- (C<sub>3-7</sub>) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group being optionally substituted by one or more substituents selected from OH, halogen, -(C<sub>1-3</sub>) alkoxy, wherein (alk) represents C<sub>1-3</sub>alkylene and n represents 0 or 1.

5 (2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C<sub>1-3</sub>)alkyl, -CO<sub>2</sub>-(C<sub>1-4</sub>)alkyl, -CO(C<sub>1-3</sub>alkyl), -S(=O)<sub>n</sub>-(C<sub>1-3</sub>alkyl), -CONR<sup>a</sup>R<sup>b</sup> (wherein R<sup>a</sup> and R<sup>b</sup> independently represent H or C<sub>1-3</sub>alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by (=O)<sub>n</sub>, where n is 1 or 2.

10 (3) Straight or branched C<sub>1-12</sub> alkyl, optionally including one or more O, S(=O)<sub>n</sub> (where n is 0, 1 or 2) or N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy or NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup> and R<sup>b</sup> both represent C<sub>1-3</sub>alkyl or hydrogen.

15 (4) a fused bicyclic aromatic ring



15

wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by -CO<sub>2</sub>-(C<sub>1-3</sub>alkyl).

20 (5) a phenyl group optionally substituted by one or more substituents selected from:

25 -halogen, -SO<sub>3</sub>H, -(alk)<sub>n</sub>OH, -(alk)<sub>n</sub>-cyano, -(O)<sub>n</sub>-(C<sub>1-6</sub>)alkyl (optionally substituted by one or more halogens), -(alk)<sub>n</sub>-nitro, -(O)<sub>m</sub>-(alk)<sub>n</sub>-CO<sub>2</sub>R<sup>c</sup>, -(alk<sub>n</sub>)-CONR<sup>c</sup>R<sup>d</sup> -(alk)<sub>n</sub>-COR<sup>c</sup>, -(alk)<sub>n</sub>-SOR<sup>e</sup>, -(alk)<sub>n</sub>-SO<sub>2</sub>R<sup>e</sup>, -(alk)<sub>n</sub>-SO<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -(alk)<sub>n</sub>OR<sup>c</sup>, -(alk)<sub>n</sub>-(CO)<sub>m</sub>-NHSO<sub>2</sub>R<sup>e</sup>, -(alk)<sub>n</sub>-NHCOR<sup>c</sup>, -(alk)<sub>n</sub>-NR<sup>c</sup>R<sup>d</sup> wherein m and n are 0 or 1 and alk represents a C<sub>1-6</sub>alkylene group or C<sub>2-6</sub> alkenyl group.

(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C<sub>1-3</sub>alkyl or NR<sup>c</sup>R<sup>d</sup>.

5 R<sup>c</sup> and R<sup>d</sup> may each independently represent hydrogen, or C<sub>1-3</sub> alkyl or when part of a group NR<sup>c</sup>R<sup>d</sup>, R<sup>c</sup> and R<sup>d</sup> together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C<sub>1-3</sub> alkyl groups.

R<sup>e</sup> represents C<sub>1-3</sub>alkyl

10 and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

15 Conveniently the adenosine A1 agonists of the general formula (I) above exhibit greater activity at the adenosine A1 receptor than the other adenosine receptor subtypes, particularly A3. More particularly the compounds exhibit little or no activity at the the A3 receptor.

20 It will be appreciated that wherein R<sup>1</sup> and/or R<sup>2</sup> in compounds of formula (I) contain one or more asymmetric carbon atoms the invention includes all diastereoisomers of compounds of formula (I) and mixtures thereof. Otherwise the stereochemical configuration of compounds of the invention is as depicted in formula (I) above.

25 As used herein, the term "alkyl" means a straight or branched chain alkyl group. Examples of suitable alkyl groups within R<sup>1</sup> and R<sup>2</sup> include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl and 2,2-dimethylpropyl.

As used herein, the term "alkylene" means a straight or branched chain alkylene group containing 1-6 carbon atoms, e.g. methylene.

As used herein, the term "C<sub>2-6</sub>alkenyl" means a straight or branched chain alkenyl group containing 2 to 6 carbon atoms. Allyl represents an example of a suitable C<sub>2-6</sub>alkenyl group.

5 The term "halogen" means fluorine, chlorine, bromine or iodine.

By aliphatic heterocyclic group is meant a cyclic group of 4-6 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatoms independently selected from nitrogen, oxygen or sulfur. This group may 10 optionally be substituted as defined hereinabove.

The term heterocyclic aromatic group refers to an aromatic mono or bicyclic ring system comprising from 5 to 10 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatoms independently selected from 15 nitrogen, oxygen and sulfur, which ring system may optionally be substituted as defined hereinabove.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. 20 Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. A particularly 25 suitable pharmaceutically acceptable salt of the compounds of formula (I) is the hydrochloride salt. Other acids such as oxalic, while not, in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. The solvates may be, for example, hydrates.

30 R<sup>3</sup> preferably represents a C<sub>1-3</sub> fluoroalkyl group especially a fluoromethyl or fluoroethyl group more preferably F<sub>2</sub>C(Me)-, FCH<sub>2</sub>-.

$R^2$  preferably represents hydrogen, methyl or halogen, more preferably hydrogen or chlorine.

Conveniently,  $R^1$  may represent  $(alk)_n-C_{3-6}$  cycloalkyl wherein  $n$  is 0 or 1 and the said cycloalkyl is either substituted by at least one substituent selected from halogen, particularly fluorine, and OH or is unsubstituted. Preferably  $n$  is zero. More preferably, the cycloalkyl group is monosubstituted with either OH or fluorine and more preferably the cycloalkyl ring has 5 carbon members.

Alternatively  $R^1$  may represent a substituted or unsubstituted aliphatic heterocyclic group, the substituent being selected from the group consisting of  $-CO_2-(C_{1-4})alkyl$ ,  $-CO-(C_{1-3})alkyl$ ,  $-S(=O)_n-(C_{1-3})alkyl$ ,  $CONR^aR^b$  (wherein  $R^a$  and  $R^b$  are defined herein above), and when there is a heteroatom S in the ring this heteroatom may optionally be substituted by  $(=O)_n$  where  $n$  is 1 or 2. More preferably the heterocyclic ring is unsubstituted or substituents are  $-CO_2-(C_{1-4})alkyl$ , or when the heteroatom is S, the substituent  $(=O)_n$  is attached to the heterocyclic sulfur atom.

Conveniently, the aliphatic heterocyclic group is unsubstituted or when the substituent is  $-CO_2(C_{1-4})alkyl$ , the heteroatom is N and the substituent is directly attached to said ring nitrogen atom.

Preferably the heterocyclic ring is 6 membered and more preferably contains only one O, N or S heteroatom.

Alternatively,  $R^1$  may represent a straight or branched alkyl of 1-6 carbon atoms optionally with at least one S  $(=O)_n$  and/or N substituted in the chain, where there is an  $S(=O)_n$  in the chain, preferably  $n$  is 1 or 2. The alkyl group conveniently may be unsubstituted or substituted by at least one OH group.

Alternatively  $R^1$  may represent a phenyl group which is substituted by one or more substituents selected from OH and halogen. Preferably the phenyl is disubstituted in the 2,4 positions. Preferably both substituents are halogen more particularly, fluorine and chlorine. For example, a particularly preferred combination is 2-fluoro and 4-chloro.

It is to be understood that the present invention covers all combinations of particular and preferred groups mentioned above.

Particular compounds according to the invention include:

5 5'-deoxy-5'-fluoro-N-(tetrahydro-pyran-4-yl)-adenosine,  
5'-deoxy-5'-fluoro-2-methyl-N-(tetrahydro-pyran-4-yl)-adenosine,  
2-chloro-5'-deoxy-5'-fluoro-N-(tetrahydro-pyran-4-yl)-adenosine,  
(2R,3R,4S,5S)-2-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-5-  
trifluoromethyl-tetrahydro-furan-3,4-diol,

10 2-chloro-5'-deoxy-5'-fluoro-N-(2R-fluoro-cyclopent-(R)-yl)-adenosine,  
2-chloro-5'-deoxy-5'-fluoro-N-(2S-hydroxy-cyclopent-(S)-yl)-adenosine,  
N-(endo-bicyclo[2.2.1]hept-2-yl)-2-chloro-5'-deoxy-5'-fluoro-adenosine,  
4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-  
purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester,

15 1-{4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-  
purin-6-ylamino]-piperidin-1-yl}-ethanone,  
N-(endo-bicyclo[2.2.1]hept-2-yl)-5'-deoxy-5'-fluoro-adenosine,  
N-(exo-bicyclo[2.2.1]hept-2-yl)-5'-deoxy-5'-fluoro-adenosine,  
5'-deoxy-5'-fluoro-N-(2S-hydroxy-cyclopent-(S)-yl)-adenosine,

20 4-[9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-  
ylamino]-piperidine-1-carboxylic acid ethyl ester,  
2-chloro-5'-deoxy-N-(1,1-dioxo-hexahydro-1.delta.6-thiopyran-4-yl)-5'-fluoro-  
adenosine,  
2-chloro-5'-deoxy-N-(2,3-dihydroxy-propyl)-5'-fluoro-adenosine,

25 25 (2R,3R,4S,5S)-2-[6-(cyclopropylmethyl-amino)-purin-9-yl]-(1,1-difluoroethyl)-  
tetrahydro-furan-3,4-diol,  
(2R,3R,4S,5S)-2-[6-(bicyclo[2.2.1]hept-2-ylamino)-purin-9-yl]-5-(1,1-difluoro-  
ethyl)-tetrahydro-furan-3,4-diol,  
2-[9-(5S-fluoromethyl-3R,4R-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-  
ylamino]-ethanesulfonic acid methylamide,

30 5'-deoxy-5'-fluoro-N-(2,2-dimethyl-propyl)-adenosine,  
N-tert-butyl-5'-deoxy-5'-fluoro-adenosine,  
5'-deoxy-5'-fluoro-N-(tetrahydro-thiopyran-4-yl)-adenosine,

2-chloro-5'-deoxy-5'-fluoro-N-isobutyl-adenosine,  
2-chloro-5'-deoxy-5'-fluoro-N-(1-methanesulfonylpiperidin-4-yl)-adenosine,  
2-Chloro-5'-deoxy-N-(2,2-dimethyl-propyl)-5'-fluoro-adenosine,  
N-(exo-Bicyclo[2.2.1]hept-2-yl)-2-chloro-5'-deoxy-5'-fluoro-adenosine,  
5 4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-  
6-ylamino]-piperidine-1-carboxylic acid butyl ester,  
5'-deoxy-N-(1,1-dioxo-hexahydro-1. $\delta$ .6-thiopyran-4-yl)-5'-fluoroadenosine  
purin-6-ylamino]-piperidine-1-carboxylic acid ethylamide,  
N-(4-chloro-2-fluoro-phenyl)-5'-deoxy-5'-fluoroadenosine,  
10 4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-  
purin-6-ylamino]piperidine-1-carboxylic acid ethylamide.

Compounds according to the invention have applicability as inhibitors of lipolysis  
i.e. they decrease plasma free fatty acid concentrations. The compounds may  
15 thus be used in the treatment of hyperlipidaemias. Furthermore, as a  
consequence of their anti-lipolytic activity, the compounds have the ability to  
lower elevated blood glucose, insulin and ketone body levels and therefore may  
be of value in the therapy of diabetes. Since anti-lipolytic agents have  
20 hypolipidaemic and hypofibrinogenaemic activity, the compounds may also  
show anti-atherosclerotic activity. The anti-lipolytic activity of compounds of the  
invention has been demonstrated by their ability to lower the concentration of  
non-esterified fatty acids (NEFA) in starved rats dosed orally according to the  
method described by P. Strong *et al.* in Clinical Science (1993), 84, 663-669.

25 In addition to their anti-lipolytic effect, the compounds of the invention may  
independently affect cardiac function by reducing heart rate and conduction.  
The compounds may thus be used in the therapy of a number of cardiovascular  
disorders, for example cardiac arrhythmias, particularly following myocardial  
infarction, and angina.

30 Furthermore, the compounds of the invention are useful as cardioprotective  
agents, having applicability in the treatment of ischaemic heart disease. As used  
herein the term "ischaemic heart disease" includes damage associated with both  
myocardial ischaemia and reperfusion, for example, associated with coronary

artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), cardioplegia, acute myocardial infarction, thrombolysis, stable and unstable angina and cardiac surgery including in particular cardiac transplantation. The compounds of the invention additionally are useful for 5 treating ischaemic damage to other organs. The compounds of the invention may also be valuable in the treatment of other disorders arising as a result of widespread atheromatous disease, for example, peripheral vascular disease (PWD) and stroke.

10 The compounds may also inhibit renin release and thus be of use in the therapy of hypertension and heart failure. The compounds may also be useful as CNS agents (e.g. as hypnotics, sedatives, analgesics and/or anti-convulsants particularly finding use in the treatment of epilepsy).

15 In addition, the compounds of the invention may find use in the treatment of sleep apnoea.

20 The compound of formula (I) and pharmaceutically acceptable acid addition salts thereof are useful as analgesics. They are therefore useful in treating or preventing pain. They may be used to improve the condition of a host, typically of a human being, suffering from pain. They may be employed to alleviate pain in a host. Thus, the compound of formula (I) and its pharmaceutically acceptable acid addition salts may be used as a preemptive analgesic to treat acute pain such as musculoskeletal pain, post operative pain and surgical pain, 25 chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis and osteoarthritis), neuropathic pain (e.g. post herpetic neuralgia, trigeminal neuralgia, neuropathies associated with diabetes and sympathetically maintained pain) and pain associated with cancer and fibromyalgia. The compound of formula (I) may also be used in the treatment or prevention of pain 30 associated with migraine, tension headache and cluster headaches and pain associated with Functional Bowel Disorders (e.g. IBS), non cardiac chest pain and non ulcer dyspepsia.

Accordingly, the invention provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or whereby the therapy involves the treatment of ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering from a CNS disorder, sleep apnoea or pain.

10 In a further aspect, the invention provides a method of treatment of a human or animal subject suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering a 15 CNS disorder or suffering from sleep apnoea or suffering pain, which method comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

20 In a further aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a human or animal suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or 25 which subject is suffering a CNS disorder or suffering from sleep apnoea or suffering pain.

30 In respect of the above mentioned ischaemic treatment, it has been found that according to a particularly unexpected aspect of the present invention, not only does administration of a compound of formula (I) prior to ischaemia provide protection against myocardial infarction, but protection is also afforded if the compound of formula (I) is administered after the ischaemic event and before reperfusion. This means that the methods of the present invention are applicable not only where ischaemia is planned or expected, for example in

cardiac surgery, but also in cases of sudden or unexpected ischaemia, for example in heart attack and unstable angina.

It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

5

In yet a further aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in association with a pharmaceutical carrier and/or excipient.

10

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in association with a pharmaceutical carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering from a CNS disorder, sleep apnoea or pain.

20

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier and/or excipient.

25

Compositions according to the invention may be formulated for topical, oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred. The compositions may be adapted for sustained release.

30

For topical administration, the pharmaceutical composition may conveniently be given in the form of a transdermal patch.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, microcrystalline cellulose or maize-starch; lubricants, for example, magnesium stearate or stearic acid; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, or carboxymethyl cellulose; emulsifying agents, for example, sorbitan mono-oleate; non-aqueous vehicles (which may include edible oils), for example, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl *p*-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

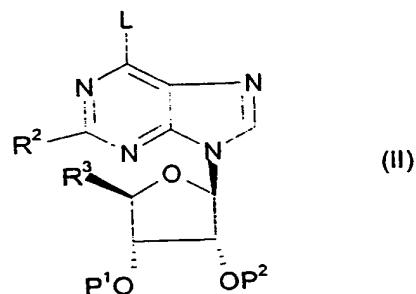
The compounds of formula (I) may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 1mg to 2g, preferably 1mg to 100mg, of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make 5 routine variations to the dosage, depending on the age and condition of the patient. The dosage will also depend on the route of administration.

In a yet further aspect the invention also provides for the use of a compound of 10 formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of human or animal subjects 15 suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease (PWD) or stroke, or which patient is suffering from a CNS disorder, sleep apnoea or pain.

The compounds of formula (I) and physiologically acceptable salts or solvates 20 thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined for compounds of formula (I) unless otherwise stated.

According to a first general process (A), a compound of formula (I) may be 25 prepared by reacting a compound of formula (II).



wherein, L represents a leaving group such as a halogen atom (e.g. a chlorine atom) and P<sup>1</sup> and P<sup>2</sup> represent hydrogen or a suitable protecting group (e.g. acetyl) with a compound of formula R<sup>1</sup>NH<sub>2</sub> or a salt thereof, under basic conditions.

5

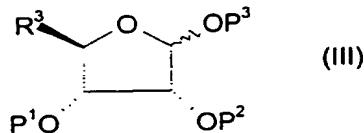
Compounds of formula (II) may be used to produce compounds of formula (I) directly by reaction with the group R<sup>1</sup>NH<sub>2</sub> either in the absence or presence of a solvent such as an alcohol (e.g. a lower alkanol such as isopropanol, t-butanol or 3-pentanol), an ether (e.g. tetrahydrofuran or dioxan), a substituted amide (e.g. dimethylformamide), a halogenated hydrocarbon (e.g. chloroform) or acetonitrile, preferably at an elevated temperature (e.g. up to the reflux temperature of the solvent), in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, or organic bases such as triethylamine, diisopropylethylamine or pyridine.

15

This reaction may be preceded or followed where appropriate by in situ removal of the P<sup>1</sup> and P<sup>2</sup> protecting groups. For example when P<sup>1</sup> and P<sup>2</sup> represent acetyl, this may be effected with an amine such as ammonia or tert-butylamine in a solvent such as methanol at a convenient temperature.

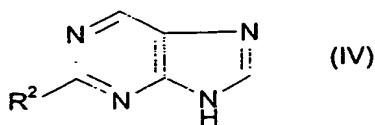
20

Compounds of formula (II) may be prepared by the reaction of a compound of formula (III)



25

wherein P<sup>3</sup> represents a suitable protecting group for example C<sub>1-3</sub>alkyl or acetyl, and P<sup>1</sup>, P<sup>2</sup> and R<sup>3</sup> are as defined above, with a compound of formula (IV)

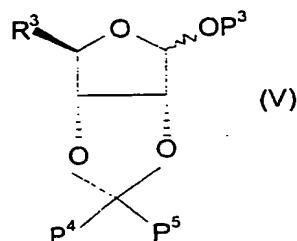


wherein L and R<sup>2</sup> are as defined above.

The reaction is conveniently carried out in a suitable solvent, such as acetonitrile in the presence of a silylating agent such as trimethylsilyl trifluoromethanesulfonate and a base such as diazabicyclo [5.4.0]undec-7-ene (DBU). Alternatively the compound of formula (IV) may first be silylated with a suitable silylating agent such as hexamethyldisilazane followed by reaction of the silylated intermediate with a compound of formula (III) and a suitable Lewis acid, for example trimethylsilyl trifluoromethanesulfonate in a suitable solvent such as acetonitrile.

Compounds of formula (IV) are either known in the art or may be prepared from known compounds using methods analogous to those used to prepare the known compounds of formula (IV).

Compounds of formula (III) may be prepared from alternative protected compounds by replacement of the alternate protecting groups with P<sup>1</sup> and P<sup>2</sup>; for example when P<sup>1</sup> and P<sup>2</sup> represent acetyl, compounds of formula (III) may be prepared from compounds of formula (V) wherein P<sup>4</sup> and P<sup>5</sup> represent C<sub>1-3</sub> alkyl and P<sup>3</sup> is as defined above by acid catalysed removal of the alkylidene protecting group, e.g. with hydrogen chloride in methanol, followed by in situ acylation for example with acetic anhydride in the presence of a base such as pyridine, in a solvent such as dichloromethane.

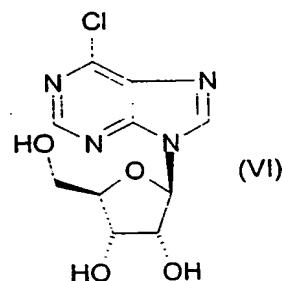


Compounds of formula (V) are known compounds or prepared by methods analogous to those used in the art to prepare the known compounds of formula V. It will be appreciated by a skilled person that the acetyl group in any of the

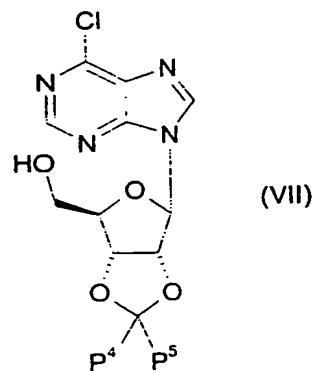
compounds above could be replaced with any suitable protecting group, for example, other esters.

5 By analogous methods, compounds of formula (I) or (II) may also be prepared from compounds wherein alkylidene groups defined by P<sup>4</sup> and P<sup>5</sup> replace P<sup>1</sup> and P<sup>2</sup>. This reaction represents an exchange of one protecting group for another and such reactions will be apparent to a person skilled in the art.

10 According to Route B, compounds of formula (II) may be prepared from 6-chloropurine riboside (VI) which is commercially available or prepared from inosine.



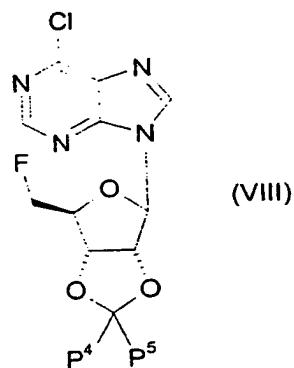
15 The first stage of the process is to protect the 2', 3'-hydroxyl groups to produce compounds of formula (VII).



20 wherein P<sup>4</sup> and P<sup>5</sup> are defined hereinabove. When the 2', 3'-hydroxyl groups are protected with an isopropylidene group (P<sup>4</sup> and P<sup>5</sup> represent methyl) this may

be effected by the use of acetone and PTSA (para-toluene sulfonic acid) or by other standard procedures using dimethoxy propane apparent to a skilled person.

5 The compound of formula (VII) is then fluorinated in a single step using TsF (para-toluenesulfonyl fluoride) and TBAF (tetra-n-butylammonium fluoride in THF (tetrahydrofuran). This forms a compound of formula (VIII).

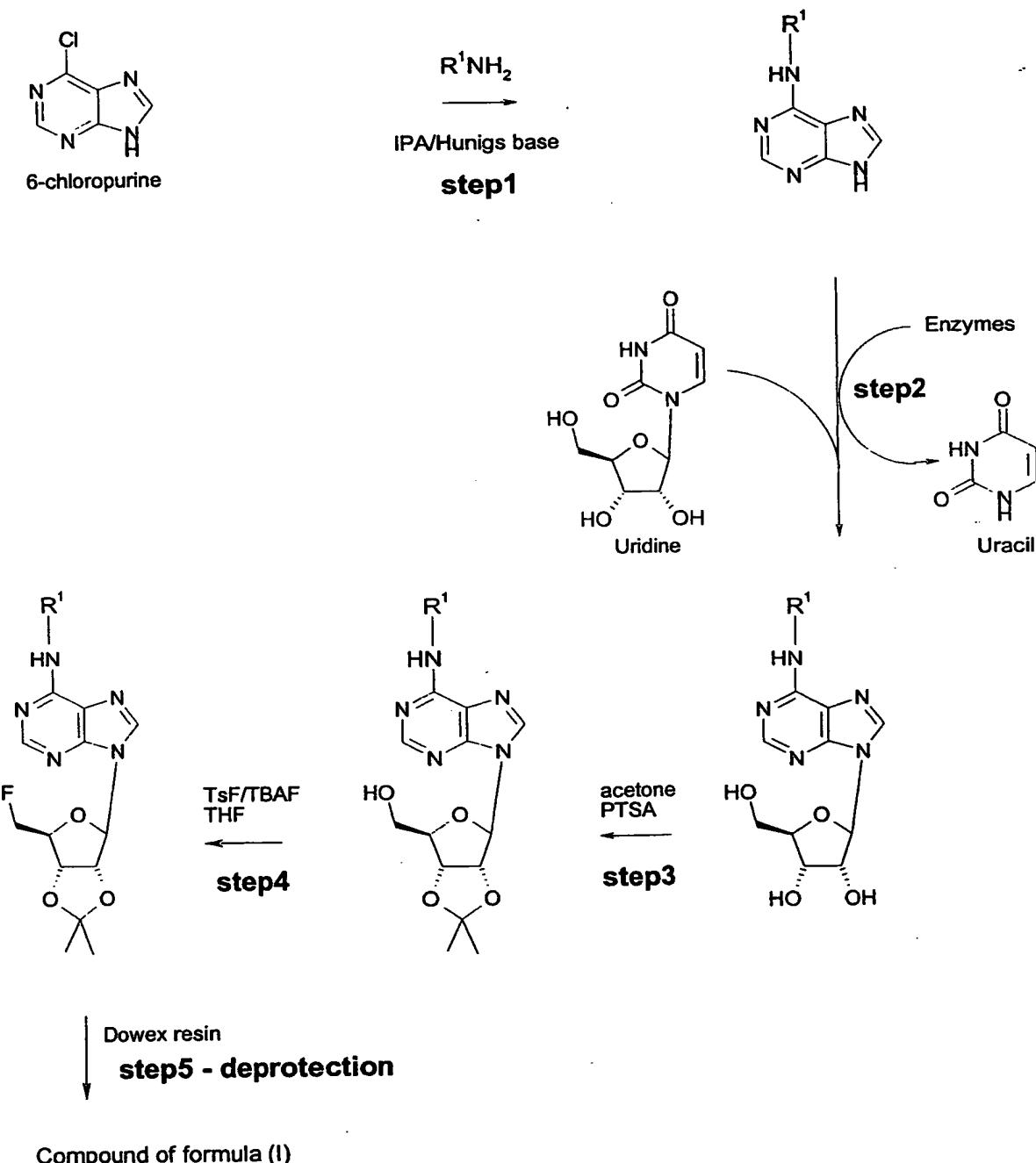


10 It will be apparent to a skilled person that the fluoroalkyl substituent at  $R^3$  may be modified at this stage. Any  $R^2$  substituent may also be introduced at an appropriate stage.

15 Finally the compound of formula (VIII) is deprotected by standard conditions e.g. acidic Dowex resin and the chlorine group is displaced by the group  $R^1NH_2$  as described hereinabove to form a compound of formula (I).

20 According to a further process (C), compounds of formula (I) may be prepared using a purine-pyrimidine transferase enzyme system. This is demonstrated schematically below:

17



This enzyme system in step 2 transfers the purine ring onto the sugar ring of uridine. As shown in the reaction scheme, the group  $\text{R}^1\text{NH}_2$  has already been

introduced by standard methods but a skilled person would appreciate this could be added at any time during the reaction scheme.

Following step 2, the sugar ring is protected by P<sup>4</sup> and P<sup>5</sup> groups as described hereinabove, for example P<sup>4</sup> and P<sup>5</sup> represent methyl, followed by fluorination of the 5'-hydroxyl group. The compound is then deprotected to produce a compound of formula (I).

This reaction scheme is intended to demonstrate the use of the enzyme system. A skilled person would be able to adapt to produce compounds of formula (I) with alternate R<sup>2</sup> and R<sup>3</sup> groups. This would be standard chemistry apparent to a person skilled in the art.

A further process (D) comprises converting a compound of formula (I) into a different compound of formula (I) by modifying the R<sup>1</sup>, R<sup>2</sup> or R<sup>3</sup> group therein.

Certain compounds of formulae (II), (III), and (V) are novel intermediates and form a further aspect of the present invention.

Compounds of the formula R<sup>1</sup>NH<sub>2</sub> are either known compounds or may be prepared from known compounds using conventional procedures with some exceptions indicated in the experimental section hereinbelow.

Specific optical isomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or where appropriate by separation of a mixture of isomers of a compound of formula (I) by conventional means e.g by fractional crystallisation or chromatography.

In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently into the form of a pharmaceutically acceptable salt. Where desired, such salts may be converted into the corresponding free bases using conventional methods.

Pharmaceutically acceptable acid addition salts of the compounds of formula (I) may be prepared by reacting a compound of formula (I) with an appropriate acid in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, 5 ethyl acetate or an alcohol (e.g. methanol, ethanol or isopropanol). Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts of the compounds 10 of formula (I), using conventional methods.

The invention is further illustrated by the following non-limiting Intermediates and Examples.

15 Standard HPLC conditions are as follows:

**Standard Automated Preparative HPLC column, conditions & eluent**

Automated preparative high performance liquid chromatography (autoprep. 20 HPLC) was carried out using a Supelco ABZ+ 5 $\mu$ m 100mmx22mm i.d. column eluted with a mixture of solvents consisting of i) 0.1% formic acid in water and ii) 0.05% formic acid in acetonitrile, the eluent being expressed as the percentage of ii) in the solvent mixture, at a flow rate of 4ml per minute. Unless otherwise stated the eluent was used as a gradient of 0-95 % (ii) over 20 25 minutes.

**LC/MS System**

Two alternative Liquid Chromatography Mass Spectroscopy (LC/MS) systems 30 were used:

***System A:***

This system used an ABZ+PLUS, 3.3cm x 4.6mm i.d. column, eluting with solvents: A - 0.1%v/v formic acid + 0.077%w/v ammonium acetate in water; and

B - 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 1ml per minute. The following gradient protocol was used: 100% A for 0.7 mins; A+B mixtures, gradient profile 0 - 100% B over 3:5mins; hold at 100% B for 3.5mins; return to 100% A over 0.3mins.

5

*System B:*

This system used an ABZ+PLUS, 3.3cm x 2.0mm i.d. column, eluting with solvents: A - 0.1%v/v formic acid + 0.077%w/v ammonium acetate in water; and B - 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 0.8ml per minute. The following gradient protocol was used: A+B mixtures, gradient profile 0 - 100% B over 3.5mins; hold at 100% B for 1.5mins; return to 100% A over 0.5mins.

10 Both systems used a micromass 'platform' spectrometer, with electrospray ionisation mode, positive and negative ion switching, mass range 80-1000 15 a.m.u.

**HPLC System**

20 The analytical HPLC system used an inertsil ODS2 150mm x 4.6mm i.d. column, eluting with solvents: A - 0.1%v/v phosphoric acid and B - 95:5 acetonitrile:water + 0.1%v/v phosphoric acid. The following gradient protocol was used with a flow rate of 1.0 mL/min: 100% A for 2 min; A+B mixtures, gradient profile 0 - 100% B over 40min; hold at 100% B for 10min.

25

Flash chromatography was carried out either on Merck silica gel (Merck 9385), or on pre-packed silica gel cartridges (Biotage).

**Intermediate 1**

30  $\beta$  anomer: Acetic acid 4R-acetoxy-2S-fluoromethyl-5R-methoxy-tetrahydro-furan-3S-yl ester

$\alpha$  anomer: Acetic acid 4R-acetoxy-2S-fluoromethyl-5S-methoxy-tetrahydro-furan-3S-yl ester

(3aS,4S,6R,6aR)-4-Fluoromethyl-6-methoxy-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole (Sharma, Moheshwar; Li, Yi X.; Ledvina, Miroslav; Bobek, Miroslav. Nucleosides Nucleotides (1995), 14(9 & 10), 1831-52.) (4.0g) was heated under reflux with conc. hydrochloric acid (0.8ml) in methanol (140ml) for 1.5h. The solvent was evaporated, more methanol (120ml) was added and heating under reflux continued overnight (16h). The solvent was again evaporated in vacuo, fresh methanol (120ml) added, and heating under reflux continued for 5h. The solvent was evaporated in vacuo and the residue azeotroped with methanol (50ml) to give the crude diol intermediate as a colourless oil (3.04g). The crude diol was dissolved in dry dichloromethane (80ml) and treated with pyridine (6.3ml) acetic anhydride (5.5ml; 5.85mmol) and 4-dimethylaminopyridine (100ml). The mixture was stirred at room temperature under nitrogen for 16h, and the solvent was evaporated in vacuo to give a pale yellow oil (4.8g). The oil was partitioned between dichloromethane and 8% aqueous sodium bicarbonate; the organic layers were washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated in vacuo to give a pale yellow oil (4.34g). Purification by flash chromatography on silica gel (Biotage), eluting with ethyl acetate:cyclohexane 25:75 and 40:60, gave the title compound ( $\alpha$  and  $\beta$  anomers).

20       $\beta$ -anomer: Colourless oil (2.2g)  
TLC  $\text{SiO}_2$  (Ethyl acetate:cyclohexane 1:2)  $R_f$ =0.4  
 $\alpha$ -anomer: Colourless oil (0.945g)  
TLC  $\text{SiO}_2$  (Ethyl acetate:cyclohexane 1:2)  $R_f$ =0.2

25      Intermediate 2  
Acetic acid 4S-acetoxy-2R-(6-chloro-purin-9-yl)-5S-fluoromethyl-tetrahydro-furan-3R-yl ester  
A suspension of 6-chloropurine (5.53g) in hexamethyldisilazane (75ml) and dry toluene (75ml) was heated under reflux under nitrogen for 2h. After cooling, the solvents were evaporated in vacuo and the residue co-evaporated with toluene (50ml). The silylated purine thus obtained was dissolved in dry acetonitrile (75ml) and acetic acid 4R-acetoxy-2S-fluoromethyl-5R-methoxy-tetrahydro-furan-3S-yl ester (3.03g) added, followed by trimethylsilyl trifluoromethanesulphonate (5.0ml). The solution was heated at 90°C for 2h,

cooled, and poured into 8% aqueous sodium bicarbonate (200ml). The mixture was extracted with ethyl acetate and the extracts dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated in vacuo. Further crude product was obtained from acetic acid 4R-acetoxy-2S-fluoromethyl-5S-methoxy-tetrahydro-furan-3S-yl ester (5.56g) and 6-chloropurine (5.53g) as described above. The crude products were combined and purified by flash chromatography on silica gel (Merck 9385), eluting with ether, to afford the title compound as a white solid (9.17g).

5 TLC  $\text{SiO}_2$  (Ether)  $R_f$ =0.2

10 **Intermediate 3**

Acetic acid 4S-acetoxy-5S-fluoromethyl-2R-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3R-yl ester

A solution of acetic acid 4S-acetoxy-2R-(6-chloro-purin-9-yl)-5S-fluoromethyl-tetrahydro-furan-3R-yl ester (3.03g) in isopropanol (120ml) was treated with 15 diisopropylethylamine (8.4ml) and 4-aminotetrahydropyran hydrochloride (Johnston, Thomas P.; McCaler, George S.; Opliger, Pamela S.; Laster, W. Russell; Montgomery, John A. Kettering-Meyer Lab., J. Med. Chem. (1971), 14(7), 600-14.) (3.26g), and the mixture was heated under reflux under nitrogen for 8h. The solution was cooled and the solvent evaporated in vacuo. The 20 residue was treated with 8% sodium bicarbonate (150ml) and extracted with ethyl acetate. The extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated in vacuo to give the title compound as a foam (3.67g).

LC/MS (System A):  $R_t$  = 3.81 min

25 **Intermediate 4 (PCT Int. Appl., WO 9507921 A1 950323.)**

Acetic acid 4S-acetoxy-2R-(2,6-dichloro-purin-9-yl)-5S-fluoromethyl-tetrahydro-furan-3R-yl ester

2,6-Dichloropurine (6.1g) was heated with hexamethyldisilazane (112ml) at 30 130°C with stirring under nitrogen for 2h. The mixture was evaporated in vacuo to give a white solid, which was azeotroped with dry toluene (80ml). The residue was treated with a solution of acetic acid 4R-acetoxy-2S-fluoromethyl-5R-methoxy-tetrahydro-furan-3S-yl ester (Intermediate 1- $\beta$  anomer) (2.5g) in dry acetonitrile (100ml) followed by trimethylsilyl trifluoromethanesulphonate (6.63ml) and the mixture was heated under reflux for 2h. The mixture was

partitioned between saturated aqueous sodium bicarbonate and dichloromethane and the organic layers washed with brine, dried ( $MgSO_4$ ) and evaporated in vacuo to give a brown gum (4.6g). Purification by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate:cyclohexane 40:60, gave the title compound as a white foam (2.67g; 64%).

5 TLC  $SiO_2$  (Ethyl acetate:cyclohexane 2:1)  $R_f$  = 0.55.

10 **Intermediate 5**

Acetic acid 4S-acetoxy-2R-(6-chloro-2-methyl-purin-9-yl)-5S-fluoromethyl-tetrahydro-furan-3R-yl ester

15 6-Chloro-2-methylpurine (Bourguignon, Jean-Jacques; Desaubry, Laurent; Raboisson, Pierre; Wermuth, Camille-Georges; Lugnier, Claire. Bourguignon, Jean-Jacques; Desaubry, Laurent; Raboisson, Pierre; Wermuth, Camille-Georges; Lugnier, Claire. Laboratoire de Pharmacochimie Moleculaire, Centre de Neurochimie, Strasbourg, 67084, Fr. J. Med. Chem. (1997), 40(12), 1768-1770. (202mg) was heated at 80°C with hexamethyldisilazane (2ml) and dry toluene (3ml) for 24h. Dry toluene (5ml) was added, the solvent was evaporated in vacuo, and the residue azeotroped with further dry toluene (5ml). A solution

20 of acetic acid 4R-acetoxy-2S-fluoromethyl-5R-methoxy-tetrahydro-furan-3S-yl ester (98mg) in dry acetonitrile (5ml) was added to the crude silylated purine, followed by trimethylsilyl trifluoromethanesulphonate (0.26ml). The mixture was heated under reflux for 4h, allowed to cool, and partitioned between saturated aqueous sodium bicarbonate (5ml) and dichloromethane (40ml). The organic

25 layer was washed with water, dried ( $MgSO_4$ ) and evaporated in vacuo to give the crude product. Purification by flash chromatography on silica gel (Merck 9385), eluting with cyclohexane:ethyl acetate (1:1), gave the title compound as a white solid (109mg).

Mass spectrum  $m/z$  387 ( $MH^+$ )

30

**Intermediate 6**

Acetic acid 4S-acetoxy-5S-fluoromethyl-2R-[2-methyl-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3R-yl ester

A solution of acetic acid 4S-acetoxy-2R-(6-chloro-2-methyl-purin-9-yl)-5S-fluoromethyl-tetrahydro-furan-3R-yl ester (108mg), 4-aminotetrahydropyran hydrochloride (153mg) and diisopropylethylamine (0.13ml) in isopropanol (10ml) was heated at 80° for 72h. The solvent was evaporated *in vacuo* to give a 5 brown semi-solid residue. Purification by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate:cyclohexane 1:1, ethyl acetate, and ethyl acetate:ethanol 10:1, gave the title compound (61mg).

Mass spectrum *m/z* 452 (MH<sup>+</sup>)

10 **Intermediate 7**

Acetic acid 4R,5-diacetoxy-2-trifluoromethyl-tetrahydro-furan-3S-yl ester

(3aR,6S,6aS)-2,2-Dimethyl-6-trifluoromethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-ol (Munier, Pascal; Picq, Dominique; Anker, Daniel. Munier, Pascal; Picq, Dominique; Anker, Daniel. Lab. Chim. Org., Univ. Claude Bernard, Villeurbanne, 69622, Fr. Tetrahedron Lett. (1993), 34(51), 8241-4.) (1.07g) was dissolved in 9:1 trifluoroacetic acid:H<sub>2</sub>O (15ml) and the solution was stirred at 22°C for 4h. The solution was concentrated *in vacuo*, followed by repeated coevaporation with toluene to give a clear, colourless gum. The gum was dissolved in dry pyridine (30ml), acetic anhydride (8.99ml) was added, and the 15 resulting solution was stirred at 22°C under N<sub>2</sub> for 3 days.

20 The pyridine and excess acetic anhydride were evaporated *in vacuo*, followed by repeated coevaporation with toluene to give a dark brown oil. Purification by flash column chromatography on silica gel (Merck 9385) eluting with cyclohexane: ethyl acetate 1:1, gave the title compound as a pale yellow gum (1.37g).

25 TLC SiO<sub>2</sub> (Ethyl acetate) R<sub>f</sub> = 0.9.

**Intermediate 8**

30 Acetic acid 4S-acetoxy-2R-(2,6-dichloro-purin-9-yl)-5S-trifluoromethyl-tetrahydro-furan-3R-yl ester

Acetic acid 4R,5-diacetoxy-2-trifluoromethyl-tetrahydro-furan-3S-yl ester (1.09g) was dissolved in anhydrous acetonitrile (5ml) and 2,6-dichloropurine (0.788g) was added, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.676ml) and trimethylsilyl trifluoromethanesulphonate (0.94ml) (TMSOTf). The resulting

solution was stirred at 22°C under nitrogen for 16h. Further 2,6-dichloropurine (200mg) was added, followed by DBU (0.17ml) and TMSOTf (0.24ml) and the mixture was stirred at 22°C under nitrogen for 4 days, followed by heating under reflux for 4h. The mixture was cooled, and partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to give a brown gum. Purification by flash column chromatography on silica gel (Merck 9385), eluting with 1:1 cyclohexane:ethylacetate, gave the title compound as a pale yellow foam (1.30g).

10 TLC  $\text{SiO}_2$  (Ethyl acetate)  $R_f$ =0.6.

#### Intermediate 9

Acetic acid 4S-acetoxy-2R-[2-chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-5S-trifluoromethyl-tetrahydro-furan-3R-yl ester

15 Acetic acid 4S-acetoxy-2R-(2,6-dichloro-purin-9-yl)-5S-trifluoromethyl-tetrahydro-furan-3R-yl ester (177mg) was heated at 60°C with 4-aminotetrahydropyran hydrochloride (110mg) and diisopropylethylamine (0.17ml) in isopropanol (5ml) for 2 days. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography on silica gel (Merck 9385), 20 eluting with ethyl acetate:cyclohexane 2:1, to give the title compound as a white foam (0.146g).

Mass Spectrum m/z 508 ( $\text{MH}^+$ ).

#### Intermediate 10

25 (3aS,4S,6R,6aR)-4-(1,1-Difluoro-ethyl)-6-methoxy-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole

A solution of 1-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-ethanone (Hampton, Alexander; Perini, Florian; Harper, Peter J. Fox Chase Cent. Hampton, Alexander; Perini, Florian; Harper, Peter J.

30 Fox Chase Cent. Cancer Med. Sci., Inst. Cancer Res., Philadelphia, Pa., USA. Carbohydr. Res. (1974), 37(2), 359-67.) (6.53g) in dichloromethane (200ml) was treated with diethylaminosulphur trifluoride (10.4ml) and the mixture was stirred at 22°C for 5 days. The solution was added carefully to 2M aqueous sodium carbonate (200ml), the mixture carefully shaken, the organic phase collected,

and the aqueous layer further extracted with dichloromethane. The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (Merck 9385) eluting with cyclohexane and cyclohexane:ether (19:1-9:1) to give the title compound as a pale yellow oil (4.72g).

5 NMR ( $\text{CDCl}_3$ )

10  $5.08 \delta(1\text{H},\text{brs},\text{CH})$ ,  $4.95 \delta(1\text{H},\text{brd},\text{CH})$ ,  $4.59 \delta(1\text{H},\text{d},\text{CH})$ ,  $4.21 \delta(1\text{H},\text{dd},\text{CH},\text{JF}-\text{C}-\text{CH}_6,2.2\text{Hz})$ ,  $3.39 \delta(3\text{H},\text{s},\text{OMe})$ ,  $1.68 \delta(3\text{H},\text{t},\text{JF}-\text{C}-\text{CH}_3)$ ,  $1.5$ ,  $1.33 \delta(2\times 3(2\times 3\text{H},\text{2xs},2\times \text{CH}_3))$ .

15

### Intermediate 11

( $\beta$  anomer): rel-Acetic acid 4R,5S-diacetoxy-2S-(1,1-difluoro-ethyl)-tetrahydro-furan-3S-yl ester

( $\alpha$  anomer): rel-Acetic acid 4R,5R-diacetoxy-2S-(1,1-difluoro-ethyl)-tetrahydro-furan-3S-yl ester

20

(3aS,4S,6R,6aR)-4-(1,1-Difluoro-ethyl)-6-methoxy-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole (4.71g) was dissolved in acetic acid:water (4:1, 125ml) and the mixture heated under reflux under nitrogen for 18h. The solvents were removed *in vacuo* and the residue was co-evaporated twice with toluene, dissolved in dichloromethane (70ml), and treated with pyridine (8ml), 4-dimethylaminopyridine (30mg) and acetic anhydride (7ml). The dark solution was allowed to stand for 41h. The solvents were removed *in vacuo* and the residue co-evaporated twice with toluene. The residue was partitioned between 8% aqueous sodium bicarbonate and dichloromethane. The organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated *in vacuo* and the residue purified by flash chromatography on silica gel (Merck 9385), eluting with cyclohexane:ether (1:1-2:3-1:4), to give the title compound ( $\beta$  anomer) : 2.51g (41%); and the title compound ( $\alpha$  anomer) : 2.13g (35%).

25 ( $\beta$  anomer): TLC  $\text{SiO}_2$  (Ether)  $R_f = 0.58$ .

30 ( $\alpha$  anomer): TLC  $\text{SiO}_2$  (Ether)  $R_f = 0.51$ .

### Intermediate 12

Acetic acid 4S-acetoxy-2R-(6-chloro-purin-9-yl)-5S-(1,1-difluoro-ethyl)-tetrahydro-furan-3R-yl ester

6-chloropurine (1.52g), hexamethyldisilazane (10ml) and toluene (50ml) were heated under reflux under nitrogen for 2h. The solvents were removed *in vacuo*, and *rel*-Acetic acid 4R,5R-diacetoxy-2S-(1,1-difluoro-ethyl)-tetrahydro-furan-3S-yl ester (2.31g) was added in dry acetonitrile (50ml), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0ml, 13.4mmol) and trimethylsilyl trifluoromethanesulphonate (4.8ml). The mixture was stirred at 22°C for 17h, then heated at 85°C for 90 min. The mixture was poured into 8% aqueous sodium bicarbonate and extracted with ethyl acetate. The organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo*, and the residue purified by flash chromatography on silica gel (Merck 9385) eluting with cyclohexane ether (1:1) and ether to give the title compound as a pale yellow gum (2.49g).

TLC  $\text{SiO}_2$  (Ether)  $R_f$  = 0.30

**Intermediate 13**

2-(2S-Hydroxy-(S)-cyclopentyl)-isoindole-1,3-dione  
(1S,2S)-2-Amino-cyclopentanol hydrochloride (1.20g) was dissolved in a solution of sodium methoxide (497mg) in methanol (10ml), filtered and evaporated *in vacuo*. The residue was dissolved in toluene (30ml) and phthalic anhydride (1.55g) added, and the mixture heated under reflux for 24h. After cooling, ethyl acetate was added and the mixture filtered. The filtrate was evaporated *in vacuo* and the residue purified by flash chromatography over silica (40g) eluting with cyclohexane-ethyl acetate (2:1) to afford the title compound as a colourless solid (1.08g).

Mass spectrum  $m/z$  232 ( $\text{MH}^+$ )

25

**Intermediate 14**

2-(2S-Fluoro-(S)-cyclopentyl)-isoindole-1,3-dione  
2-(2S-hydroxy-(S)-cyclopentyl)-isoindole-1,3-dione (3.42g) was dissolved in dry dichloromethane (55ml) and diethylaminosulfur trifluoride (3.43ml) added, and the solution stirred under reflux under nitrogen for 72h. The solution was poured carefully into 8% sodium bicarbonate solution (100ml) and the organic phase separated. The aqueous phase was further extracted with dichloromethane and the combined organic layers dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo*. The residue was purified by flash chromatography over silica (100g) eluting with

cyclohexane-ethyl acetate (1:1) to give the title compound as a cream powder (1.25g).

Mass spec  $m/z$  234 ( $\text{MH}^+$ ), 251 ( $\text{MNH}_4^+$ )

5 **Intermediate 15**

(1S,2S)-2-Fluorocyclopentylamine hydrochloride

2-(2S-fluoro-(S)-cyclopentyl)-isoindol-1,3-dione (6.75g), hydrazine hydrate (1.55ml) and ethanol (200ml) were treated with water (1.55ml) and heated under reflux for 4h. The mixture was cooled to 20°C, filtered and the filtrate treated with conc. hydrochloric acid to pH1. The solution was evaporated *in vacuo* and taken up in water, filtered, and the filtrate evaporated *in vacuo*. The residue was recrystallised (with hot filtration) from ethyl acetate-methanol (3:1) to afford the title compound as an off-white solid (2.59g).

10  $\text{NMR}$   $\delta$ (DMSO) 8.3 (3H, brs,  $-\text{NH}_3^+$ ), 5.04, (1H, dm,  $\text{CHF}$ ,  $J$  F-C-H, 52Hz), 3.49 (1H, brdm,  $\text{CH}$ ,  $J$  F-C-C-H 20Hz), and 2.2-1.4 (6Hm, 3x $\text{CH}_2$ ).

15 **Example 1**

5'-Deoxy-5'-fluoro-N-(tetrahydro-pyran-4-yl)-adenosine

A solution of acetic acid 4S-acetoxy-5S-fluoromethyl-2R-[6-tetrahydro-pyran-4-yl 20 amino)-purin-9-yl]-tetrahydro-furan-3R-yl ester (3.67g) in methanol (120ml) was treated with a solution of potassium carbonate (3.50g) in water (ca. 15ml) and the mixture was stirred at 23°C for 17h. The resulting solution was applied directly onto silica gel (20g) and purified by flash chromatography on silica gel (Merck 9385), eluting with dichloromethane:methanol (10:1), to give the title 25 compound as a colourless solid (2.16g).

Recrystallisation from ethanol (75ml) gave the title compound as a colourless solid (1.48g).

LC/MS (System A):  $R_t$  = 3.25 min.

Mass spectrum  $m/z$  360 ( $\text{MH}^+$ )

30

**Example 2**

5'-Deoxy-5'-fluoro-2-methyl-N-(tetrahydro-pyran-4-yl)-adenosine

Acetic acid 4S-acetoxy-5S-fluoromethyl-2R-[2-methyl-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3R-yl ester (56mg) was stirred with

potassium carbonate (42mg) in methanol (2ml) and water (2ml) at 22°C for 24h. The solvent was evaporated in vacuo, and the residue purified by flash chromatography on silica gel (Merck 9385), eluting with dichloromethane:ethanol:880 ammonia (100:10:1), to give the title compound as a white solid (44mg).

5 TLC SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>:EtOH:880 ammonia, 100:10:1) R<sub>f</sub> = 0.25.  
Mass spectrum m/z 368 (MH<sup>+</sup>)

#### Example 3

10 2-Chloro-5'-deoxy-5'-fluoro-N-(tetrahydro-pyran-4-yl)-adenosine  
Acetic acid 4S-acetoxy-2R-(2,6-dichloro-purin-9-yl)-5S-fluoromethyl-tetrahydro-furan-3R-yl ester (50mg) was heated at 55-58°C with 4-aminotetrahydropyran hydrochloride (33mg) and diisopropylethylamine (0.125ml) in isopropanol (5ml) for 21h. On cooling to room temperature, methanolic ammonia (4ml) was added, and the mixture was allowed to stand at room temperature (22°C) overnight (16h). The mixture was evaporated to dryness in vacuo to give the crude product which was purified by solid phase extraction (5g, Varian Mega Bondelut cartridge, aminopropyl bonded phase, eluting with (i) CHCl<sub>3</sub>, (ii) acetone, to give the title compound (47mg).

15 TLC SiO<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>:MeOH 9:1) R<sub>f</sub> = 0.5  
Mass spectrum m/z 388 (MH<sup>+</sup>)

#### Example 4

20 (2R,3R,4S,5S)-2-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-5-trifluoromethyl-tetrahydro-furan-3,4-diol  
Acetic acid 4S-acetoxy-2R-[2-chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-5S-trifluoromethyl-tetrahydro-furan-3R-yl ester (141mg) was stirred at room temperature with potassium carbonate (115mg) in 2:1 methanol:water (6ml) for 17h. The solvent was evaporated in vacuo to give a yellow solid (0.274g).  
25 Purification by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate and ethyl acetate:methanol 9:1, gave the title compound as a white solid (96mg).

TLC SiO<sub>2</sub> (Ethyl acetate) R<sub>f</sub> = 0.25.

### Mass Spectrum $m/z$ 424 ( $\text{MH}^+$ ).

### Example 5

Example 3 (2R,3R,4S,5S)-2-[6-(Bicyclo[2.2.1]hept-2-ylamino)-purin-9-yl]-5-(1,1-difluoroethyl)-tetrahydro-furan-3,4-diol

5 ethyl)-tetrahydro-furan-3,4-diol  
Acetic acid 4S-acetoxy-2R-(6-chloro-purin-9-yl)-5S-(1,1-difluoro-ethyl)-  
tetrahydro-furan-3R-yl ester (70mg) was heated at 80-85°C with (±)-endo-  
norbornylamine hydrochloride and N,N-diisopropylethylamine (0.18ml) in  
isopropanol (5ml) for 24h. The solvent was evaporated to Ca 1ml volume,  
methanolic ammonia (3ml) added, and the mixture was allowed to stand for 17h.  
10 The solvent was evaporated and the residue purified by solid phase extraction  
(Varian Bondelut cartridge, aminopropyl bonded phase) eluting with chloroform  
(to elute excess amine) followed by ethyl acetate:methanol 9:1, to give the title  
compound (0.025g).

15 Mass Spectrum  $m/z$  396 ( $MH^+$ ).

### NMR (MeOD)

**NMR (MeOD)** 8.22  $\delta$ (1H,s,heterocyclic CH), 8.17  $\delta$ (1H,s,heterocyclic CH), 6.08  $\delta$ (1H,d,CH), 4.64  $\delta$ (1H,t,CH), 4.49  $\delta$ (1H,dd,CH), 4.40  $\delta$ (1H,vbrs,CH), 4.15  $\delta$ (1H,ddd,CH) JF-  
C-CH<sub>7,17H<sub>3</sub></sub>, 2.57  $\delta$ (1H,brt,CH), 2.3-2.08  $\delta$ (2H,brt+m,2xCH), 1.8-1.5  
s(6H t+3xCH), 1.5-1.3  $\delta$ (3H,m,3xCH), 1.04  $\delta$ (1H,ddd,CH).

By analogous methods, the following examples were synthesised:-

### Example 6

25 2-Chloro-5-deoxy-5'-fluoro-N-(2R-fluoro-cyclopent-(R)-yl)-adenosine

Prepared from Intermediate 4 (as Example 3)

Prepared from intermediate (1)

Mass spectrum,  $m/z$  390 ( $M\ddagger$ )

30 **Example 7**  
2-Chloro-5'-deoxy-5'-fluoro-N-(2S-hydroxy-cyclopent-(S)-yl)adenosine  
Prepared from Intermediate 4 as (Ex 3)  
LC/MS (system A):  $R_t = 3.55$  min  
Mass spectrum  $m/z$  388 ( $MH^+$ ).

**Example 8****N-(endo-Bicyclo[2.2.1]hept-2-yl)-2-chloro-5'-deoxy-5'-fluoro-adenosine**

Prepared from Intermediate 4 (as Ex.3)

5 LC/MS (system A):  $R_t$  = 4.32min

Mass spectrum  $m/z$  398 ( $MH^+$ )

**Example 9****4-[2-Chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-**

10 **purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester**

From Intermediate 4 (as Ex.3)

LC/MS (system A):  $R_t$  = 3.90min

Mass spectrum  $m/z$  459 ( $MH^+$ )

15 **Example 10**

**1-[4-[2-Chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidin-1-yl]-ethanone**

From Intermediate 4 (as Ex.1)

LC/MS (system A):  $R_t$  = 3.67min

20 Mass spectrum  $m/z$  429 ( $MH^+$ )

**Example 11****N-(endo-Bicyclo[2.2.1]hept-2-yl)-5'-deoxy-5'-fluoro-adenosine**

From Intermediate 2 (as Ex.1)

25 LC/MS (system A):  $R_t$  = 4.05min

Mass spectrum  $m/z$  364 ( $MH^+$ )

**Example 12****N-(exo-Bicyclo[2.2.1]hept-2-yl)-5'-deoxy-5'-fluoro-adenosine**

30 From Intermediate 2 (as Ex.1)

Mass spectrum  $m/z$  364 ( $MH^+$ )

HPLC  $R_t$  = 14.8min

**Example 13**

5'-Deoxy-5'-fluoro-N-(2S-hydroxy-cyclopent-(S)-yl)-adenosine

From Intermediate 2 (as Ex.1)

Mass spectrum  $m/z$  354 ( $\text{MH}^+$ )

HPLC  $R_t$  = 10.3min

5

Example 144-[9-(5S-Fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester

From Intermediate 2 (as Ex.1)

10 Mass spectrum  $m/z$  425 ( $\text{MH}^+$ )

HPLC  $R_t$  = 14.0min

Example 152-Chloro-5'-deoxy-N-(1,1-dioxo-hexahydro-1.delta.6-thiopyran-4-yl)-5'-fluoro-

15 adenosine

From Intermediate 4 (as Ex.3)

LC/MS (system A):  $R_t$  = 3.66min

Mass spectrum  $m/z$  436 ( $\text{MH}^+$ )

20

Example 162-Chloro-5'-deoxy-N-(2,3-dihydroxy-propyl)-5'-fluoro-adenosine

From Intermediate 4 (as Ex.3)

LC/MS (system A):

$R_t$  = 3.07min

25 Mass spectrum  $m/z$  378 ( $\text{MH}^+$ )

Example 17(2R,3R,4S,5S)-2-[6-(Cyclopropylmethyl-amino)-purin-9-yl]-(1,1-difluoro-ethyl)-tetrahydro-furan-3,4-diol

30 From Intermediate 12 (as Ex.5)

Mass spectrum  $m/z$  356 ( $\text{MH}^+$ )

LC/MS (system A):  $R_t$  = 3.73min

Example 18

2-[9-(5S-Fluoromethyl-3R,4R-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-ethanesulfonic acid methylamide

From Intermediate 2 (as Ex.1)

Mass spectrum  $m/z$  391 ( $\text{MH}^+$ )

5 HPLC  $R_t$  = 10.1min

**Example 19**

5'-Deoxy-5'-fluoro-N-(2,2-dimethyl-propyl)-adenosine

From Intermediate 2 (as Ex.1)

10 LC/MS (system A):  $R_t$  = 4.26min

Mass spectrum  $m/z$  340 ( $\text{MH}^+$ )

**Example 20**

N-tert-Butyl-5'-deoxy-5'-fluoro-adenosine

15 From Intermediate 2 (as Ex.1)

LC/MS (system A):  $R_t$  = 4.29min

Mass spectrum  $m/z$  326 ( $\text{MH}^+$ )

**Example 21**

5'-Deoxy-5'-fluoro-N-(tetrahydro-thiopyran-4-yl)-adenosine

From Intermediate 2 (as Ex.1)

LC/MS (system A):  $R_t$  = 4.09min

Mass spectrum  $m/z$  370 ( $\text{MH}^+$ )

25 **Example 22**

2-Chloro-5'-deoxy-5'-fluoro-N-isobutyl-adenosine

From Intermediate 4 (as Ex.3)

LC/MS (system A):  $R_t$  = 4.61min

Mass spectrum  $m/z$  360 ( $\text{MH}^+$ )

30

**Example 23**

2-Chloro-5'-deoxy-5'-fluoro-N-(1-methanesulfonyl-piperidin-4-yl)-adenosine

From Intermediate 4 (as Ex.3)

LC/MS (system A):  $R_t$  = 4.22min

Mass spectrum  $m/z$  465 ( $\text{MH}^+$ )

**Example 24**

2-Chloro-5'-deoxy-N-(2,2-dimethyl-propyl)-5'-fluoro-adenosine

5 From Intermediate 4 (as Ex.3)  
LC/MS (system A):  $R_t = 4.77\text{min}$   
Mass spectrum  $m/z$  374 ( $\text{MH}^+$ )

**Example 25**

N-(exo-Bicyclo[2.2.1]hept-2-yl)-2-chloro-5'-deoxy-5'-fluoro-adenosine

10 From Intermediate 4 (as Ex.3)  
LC/MS (system A):  $R_t = 4.92\text{min}$   
Mass spectrum  $m/z$  398 ( $\text{MH}^+$ )

15 **Example 26**

4-[2-Chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid butyl ester

From Interm. 4 (as Ex.3)  
LC/MS (system A):  $R_t = 4.84\text{min}$   
Mass spectrum  $m/z$  487 ( $\text{MH}^+$ )

**Example 27**

5'-Deoxy-N-(1,1-dioxo-hexahydro-1. $\delta$ .6-thiopyran-4-yl)-5'-fluoro-adenosine

From Intermediate 2 (as Ex.1)  
LC/MS (system A):  $R_t = 3.64\text{min}$   
Mass spectrum  $m/z$  402 ( $\text{MH}^+$ )

**Example 28**

N-(4-Chloro-2-fluoro-phenyl)-5'-deoxy-5'-fluoro-adenosine

30 From Intermediate 2 (as Ex.1)  
Mass spectrum  $m/z$  398 ( $\text{MH}^+$ )  
LC/MS (system A):  $R_t = 4.03\text{min}$

**Example 29**

4-[2-Chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethylamide

From Intermediate 4 (as Ex.3)

LC/MS (system A):  $R_t = 4.04\text{min}$

5 Mass spectrum  $m/z 458 (\text{MH}^+)$

Reporter Gene Experiments

Agonist activity was measured in Chinese hamster ovary (CHO) cells containing the CRE/SPAP/HYG (CRE = cyclic AMP response element; HYG = hygromycin resistance; SPAP = secreted placental alkaline phosphatase) reporter gene elements, which upon stimulation of cAMP levels produced SPAP. A cell line was used, which was stably transfected with either the human adenosine A1 receptor or the human adenosine A3 receptor in addition to the above elements.

10 Cells were plated out in 96-well plates in culture medium and incubated at 37°C for 1 hour. For measurement of potency, agonists were added to the appropriate wells at a concentration range of approximately  $10^{-10} - 10^{-5}\text{M}$ . 15Min later, cAMP levels were stimulated by addition of a maximal concentration of forskolin. All cells were then incubated for a further 5 hours at 37°C, and cooled

15 to room temperature, after which a substrate for the phosphatase (para-nitrophenol phosphate, pNPP); which is converted by SPAP to a coloured reagent) was then added and the 96-well plates were read in a plate reader. From these readings, the concentration-dependence of the inhibition by the agonist for forskolin-stimulated SPAP production can be calculated. One of the

20 agonists tested on each 96-well plate was the standard non-selective agonist, N-ethylcarboxamidoadenosine (NECA), and the potency of all test agonists is expressed relative to that of the NECA standard.

(ECR = equipotent concentration ratio relative to NECA = 1)

Table 1:

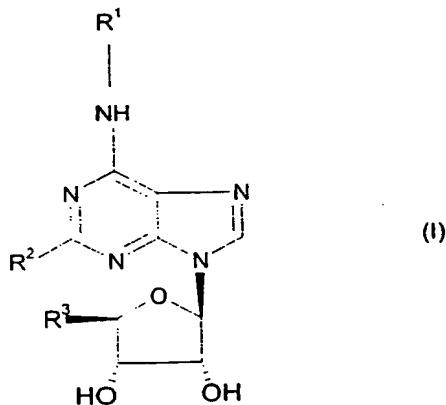
Biological Data: A1, A3 Receptor, Reporter Gene Assay ECR

<u>Example</u>	<u>A1</u>	<u>A3</u>
1	1.9	>226.00
2	11.8	>226.00
3	2.41	>139.00
4	190.10	
5	7.14	>257.00
6	0.91	>156.00
7	0.45	>91.00
8	0.21	>91.00
9	3.00	>129.00
10	66.80	>162.00
11	0.47	>152.00
12	0.54	>152.00
13	1.47	>435.00
14	1.68	>435.00
15	9.16	>240.00
16	7.29	>353.00
17	22.30	>353.00
18	0.71	>353.00
19	3.51	>353.00
20	8.17	>353.00
21	1.64	>145.00
22	3.30	48.90
23	11.20	>233.00
24	7.83	>151.00
25	0.78	>233.00
26	4.50	>162.00
27	6.20	>170.00
28	2.05	>236.00
29	51.60	

CLAIMS

1. A compound of formula (I) which is an agonist at the adenosine A1 receptor

5



wherein R<sup>2</sup> represents C<sub>1-3</sub>alkyl, halogen or hydrogen;

10 R<sup>3</sup> represents a fluorinated straight or branched alkyl group of 1-6 carbon atoms;

*R1 = sub. 5.1 !?*

(1) -(alk)<sub>n</sub>- (C<sub>3-7</sub>) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C<sub>1-3</sub>) alkoxy, wherein (alk) represents C<sub>1-3</sub>alkylene and n represents 0 or 1.

15

20

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C<sub>1-3</sub>)alkyl, -CO<sub>2</sub>(C<sub>1-4</sub>)alkyl, -CO(C<sub>1-3</sub>alkyl), -S(=O)<sub>n</sub>-(C<sub>1-3</sub>alkyl), -CONR<sup>a</sup>R<sup>b</sup> (wherein R<sup>a</sup> and R<sup>b</sup> independently represent H or C<sub>1-3</sub>alkyl) or =O; and where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by (=O)<sub>n</sub>, where n is 1 or 2.

5 (3) Straight or branched C<sub>1-12</sub> alkyl, optionally including one or more O, S(=O)<sub>n</sub> (where n is 0, 1 or 2), or N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy or NR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup> and R<sup>b</sup> both represent C<sub>1-3</sub>alkyl or hydrogen.

(4) a fused bicyclic aromatic ring



10 (5) wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by -CO<sub>2</sub> -(C<sub>1-3</sub>alkyl).

15 (5) a phenyl group optionally substituted by one or more substituents selected from:

20 (5) -halogen, -SO<sub>3</sub>H, -(alk)<sub>n</sub>-OH, -(alk)<sub>n</sub> -cyano, -(O)<sub>n</sub> -(C<sub>1-6</sub>)alkyl (optionally substituted by one or more halogens), - (alk)<sub>n</sub> -nitro, -(O)<sub>m</sub> -(alk)<sub>n</sub>- CO<sub>2</sub>R<sup>c</sup>, -(alk<sub>n</sub>)- CONR<sup>c</sup>R<sup>d</sup>, -(alk)<sub>n</sub> -COR<sup>c</sup>, -(alk)<sub>n</sub> -SOR<sup>e</sup>, -(alk)<sub>n</sub> -SO<sub>2</sub>R<sup>e</sup>, -(alk)<sub>n</sub> -SO<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -(alk)<sub>n</sub>-OR<sup>c</sup>, -(alk)<sub>n</sub> -(CO)<sub>m</sub>- NSO<sub>2</sub>R<sup>e</sup>, -(alk)<sub>n</sub> - NHCOR<sup>c</sup>, -(alk)<sub>n</sub> - NR<sup>c</sup>R<sup>d</sup> wherein m and n are 0 or 1 and alk represents a C<sub>1-6</sub>alkylene group or C<sub>2-6</sub> alkenyl group.

25 (6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C<sub>1-3</sub>alkyl or NR<sup>c</sup>R<sup>d</sup>.

(6) R<sup>c</sup> and R<sup>d</sup> may each independently represent hydrogen, or C<sub>1-3</sub> alkyl or when part of a group NR<sup>c</sup>R<sup>d</sup>, R<sup>c</sup> and R<sup>d</sup> together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C<sub>1-3</sub> alkyl groups.

$R^e$  represents  $C_{1-3}$ alkyl

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

2. A compound according to claim 1 wherein  $R^3$  represents a  $C_{1-3}$  fluoroalkyl group.
- 5 3. A compound according to claim 2 wherein  $R^3$  represents  $F_2C(Me)$ - or  $FCH_2$ -.
4. A compound according to any of claims 1-3 wherein  $R^2$  represents H, methyl or halogen.
- 10 5. A compound according to claim 4 wherein  $R^2$  represents H or chlorine.
6. A compound according to any of claims 1-5 wherein  $R^1$  represents  $(alk)_n$  -  $C_{3-6}$ - cycloalkyl wherein n is 0 and 1 and the cycloalkyl is substituted by at least one substituent selected from halogen, OH or is unsubstituted.
7. A compound according to claim 6 wherein n represents zero.
- 15 8. A compound according to claim 6 or 7 wherein the cycloalkyl is 5 membered and is monosubstituted with OH or fluorine.
9. A compound according to any of claims 1 to 5 wherein  $R^1$  represents a substituted or unsubstituted aliphatic heterocyclic group, the substituent being selected from the group consisting of  $-CO_2$   $-(C_{1-4})$ alkyl,  $-CO-(C_{1-3})$ alkyl,  $-S(=O)_n-(C_{1-3})$ alkyl,  $CONR^aR^b$  (wherein  $R^a$  and  $R^b$  are defined in claim 1, and when there is a heteroatom S in the ring this heteroatom may 20 optionally be substituted by  $(=O)_n$  where n is 1 or 2.
10. A compound according to claim 9 wherein the heterocyclic ring is unsubstituted or substituted with  $-CO_2-(C_{1-4})$ alkyl, or when the heteroatom is S, the substituent  $(=O)_n$  is attached to the heterocyclic sulfur atom.

11. A compound according to claim 9 wherein the heteroatom is N and the substituent is  $\text{CO}_2(\text{C}_{1-4}\text{)alkyl}$  is attached to the N atom.
12. A compound according to claims 9-11 wherein the heterocyclic ring is 6 membered and contains only one heteroatom.
- 5 13. A compound according to any of claims 1-5 wherein  $\text{R}^1$  represents a substituted or unsubstituted straight or branched alkyl of 1-6 carbon atoms, optionally with at least one  $\text{S}(\text{=O})_n$  and/or N substituted in the chain, and n is 1 or 2.
- 10 14. A compound according to claim 13 wherein the alkyl group is substituted by at least one OH group.
- 15 15. A compound according to any of claims 1 to 5 wherein  $\text{R}^1$  represents a phenyl group substituted by one or more substituents selected from OH or halogen.
16. A compound according to claim 15 wherein the phenyl group is disubstituted in the 2,4 positions.
17. A compound according to claim 16 wherein both substituents are halogen.
18. A compound according to claim 17 wherein the 2 substituent is fluoro and the 4 substituent is chloro.
19. A compound according to claim 1 which is
- 20 5'-deoxy-5'-fluoro-N-(tetrahydro-pyran-4-yl)-adenosine,  
5'-deoxy-5'-fluoro-2-methyl-N-(tetrahydro-pyran-4-yl)-adenosine,  
2-chloro-5'-deoxy-5'-fluoro-N-(tetrahydro-pyran-4-yl)-adenosine,  
(2R,3R,4S,5S)-2-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-5-trifluoromethyl-tetrahydro-furan-3,4-diol,
- 25 2-chloro-5'-deoxy-5'-fluoro-N-(2R-fluoro-cyclopent-(R)-yl)-adenosine,  
2-chloro-5'-deoxy-5'-fluoro-N-(2S-hydroxy-cyclopent-(S)-yl)-adenosine,  
N-(endo-bicyclo[2.2.1]hept-2-yl)-2-chloro-5'-deoxy-5'-fluoro-adenosine,

4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester,  
1-{4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidin-1-yl}-ethanone,  
5 N-(endo-bicyclo[2.2.1]hept-2-yl)-5'-deoxy-5'-fluoro-adenosine,  
N-(exo-bicyclo[2.2.1]hept-2-yl)-5'-deoxy-5'-fluoro-adenosine,  
5'-deoxy-5'-fluoro-N-(2S-hydroxy-cyclopent-(S)-yl)-adenosine,  
4-[9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester,  
10 2-chloro-5'-deoxy-N-(1,1-dioxo-hexahydro-1.delta.6-thiopyran-4-yl)-5'-fluoro-adenosine,  
2-chloro-5'-deoxy-N-(2,3-dihydroxy-propyl)-5'-fluoro-adenosine,  
(2R,3R,4S,5S)-2-[6-(cyclopropylmethyl-amino)-purin-9-yl]-(1,1-difluoroethyl)-tetrahydro-furan-3,4-diol,  
15 (2R,3R,4S,5S)-2-[6-(bicyclo[2.2.1]hept-2-ylamino)-purin-9-yl]-5-(1,1-difluoro-ethyl)-tetrahydro-furan-3,4-diol,  
2-[9-(5S-fluoromethyl-3R,4R-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-ethanesulfonic acid methylamide,  
5'-deoxy-5'-fluoro-N-(2,2-dimethyl-propyl)-adenosine,  
20 N-tert-butyl-5'-deoxy-5'-fluoro-adenosine,  
5'-deoxy-5'-fluoro-N-(tetrahydro-thiopyran-4-yl)-adenosine,  
2-chloro-5'-deoxy-5'-fluoro-N-isobutyl-adenosine,  
2-chloro-5'-deoxy-5'-fluoro-N-(1-methanesulfonylpiperidin-4-yl)-adenosine,  
2-Chloro-5'-deoxy-N-(2,2-dimethyl-propyl)-5'-fluoro-adenosine,  
25 N-(exo-Bicyclo[2.2.1]hept-2-yl)-2-chloro-5'-deoxy-5'-fluoro-adenosine,  
4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-  
6-ylamino]-piperidine-1-carboxylic acid butyl ester,  
5'-deoxy-N-(1,1-dioxo-hexahydro-1.delta.6-thiopyran-4-yl)-5'-  
30 fluoroadenosine  
purin-6-ylamino]-piperidine-1-carboxylic acid ethylamide;  
N-(4-chloro-2-fluoro-phenyl)-5'-deoxy-5'-fluoroadenosine,  
4-[2-chloro-9-(5S-fluoromethyl-3R,4S-dihydroxy-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]piperidine-1-carboxylic acid ethylamide.

20. A compound according to claim 1 which exhibits little or no activity at the adenosine A3 receptor.

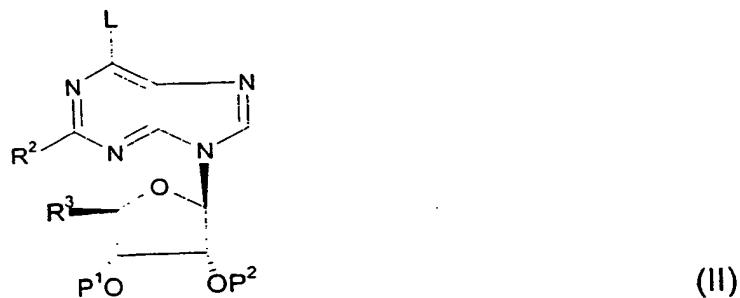
21. A compound according to any of claims 1-20 for use in therapy.

22. A pharmaceutical composition comprising a compound according to any of claims 12-20 together with a pharmaceutical carrier and/or excipient.

5 23. Use of a compound according to any of claims 1-20 for the manufacture of a medicament for the treatment of a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder or sleep apnoea.

10 24. A method of treating a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration or reducing heart rate or which patient is suffering from or is susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which patient is suffering pain, a CNS disorder or sleep apnoea.

15 25. A process for the preparation of a compound according to claims 1-20 which comprises reacting a compound of formula (II).



wherein L represents a leaving group, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1 and P<sup>1</sup> and P<sup>2</sup> represent hydrogen or a protecting group, with a compound of formula R<sup>1</sup>NH<sup>2</sup> or a salt thereof under basic conditions,

**THIS PAGE BLANK (USPTO)**

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/07021

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C07H19/16 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 33591 A (NOVONORDISK AS) 18 September 1997	1-5, 9, 10, 12, 20-24 1-25
Y	see the whole document, but in particular, examples 40 and 41, and the table on page 17	
X	WO 95 07921 A (NOVONORDISK AS ; LAU JESPER (DK); KNUTSEN LARS JACOB STRAY (DK)) 23 March 1995	1-5, 9, 10, 12, 20-24
Y	see page 13, line 1 - line 8; examples 18, 19	1-25
	---	
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 June 1999

Date of mailing of the international search report

18/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Scott, J

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 98/07021

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MOOS W H ET AL: "N6-CYCLOALKYLADENOSINES. POTENT A1-SELECTIVE ADENOSINE AGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 10, 1 October 1985, page 1383/1384 XP002038896 see the whole document	1-25
Y	LUBITZ VON D K J E ET AL: "REDUCTION OF POSTICHEMIC BRAIN DAMAGE AND MEMORY DEFICITS FOLLOWING TREATMENT WITH THE SELECTIVE ADENOSINE A1 RECEPTOR AGONIST" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 302, no. 1/03, 1 January 1996, pages 43-48, XP002035719 see abstract	1-25
A	US 3 575 959 A (SHEN TSUNG-YING ET AL) 20 April 1971 see example 24	1
P, Y	WO 97 43300 A (GLAXO GROUP LTD ; ELLIS FRANK (GB); SWANSON STEPHEN (GB); COUSINS R) 20 November 1997 see the whole document, but especially claim 1; and page 28, table 2	1-25

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/07021

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: **24**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark:** Although claim 24  
is directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP 98/07021

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9733591 A	18-09-1997	AU	2022497 A		01-10-1997
		AU	2022597 A		01-10-1997
		WO	9733590 A		18-09-1997
WO 9507921 A	23-03-1995	AU	678053 B		15-05-1997
		AU	7651994 A		03-04-1995
		CA	2171940 A		23-03-1995
		EP	0719275 A		03-07-1996
		FI	961219 A		15-05-1996
		NO	961071 A		15-05-1996
		NZ	273284 A		24-03-1997
		US	5589467 A		31-12-1996
		ZA	9407201 A		18-03-1996
US 3575959 A	20-04-1971	NONE			
WO 9743300 A	20-11-1997	AU	2896197 A		05-12-1997
		EP	0901499 A		17-03-1999